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Pulmonary embolism in pregnancy and the puerperium

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A B S T R A C T

Pulmonary embolism (PE) in pregnant women appears to be increasing. This could be related in part to improved health care allowing more women with risk factors to conceive, as well as increase in the high-risk groups which include pregnancies conceived on artificial reproductive technology, advancing maternal age, obesity, and caesarean deliveries. Prevention and early diagnosis with prompt effective treatment can reduce maternal mortality and improve pregnancy outcome, so that obstetricians should be on the lookout for venous thrombosis and PE, especially when in the majority of cases, risk factors only start to emerge or develop in the course of pregnancy and delivery. Management includes accurate diagnosis with ventilation/perfusion scan and CT pulmonary angiography, followed by effective anticoagulation and more aggressive measures such as thrombolysis as indicated, together with general supportive measures. Postpartum management should cover subsequent health issues, including breastfeeding, contraception, mood changes, and recurrence in subsequent pregnancies.

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Epidemiology

Venous thromboembolism (VTE) is usually considered as one serious and life-threatening complication in pregnant and postpartum women, but there are two components, namely deep vein

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thrombosis (DVT) and pulmonary embolism (PE). The prevalence of pregnancy-associated (PA) VTE is around 1–2/1000 pregnancies [1,2], and that for PA-PE is between 1 in 1000–3000 [3]. The most severe form of PE is massive PE with extensive pulmonary artery obstruction, haemodynamic instability, and an in-hospital mortality of 7% [3]. Globally, PE caused 3% of all maternal deaths [4]. In developed countries, PE is a leading cause of direct maternal deaths with an incidence of 1.08/100,000 maternities [1] and causes 10–15% of all maternal deaths in Europe and North America [3,4]. In the USA, PE had increased from 15.6/100,000 vaginal deliveries in 2006 to 29.8/100,000 in 2012, contributing to 9.2% of maternal deaths [5]. In a UK review of 143 cases of antenatal PE, the case fatality rate was 3.5% [6]. A contributing factor is substandard care, identified in more than half of all deaths from PE in the UK [4].

Pregnancy predisposes toward increased DVT due to factors including hypercoagulability (increased clotting factors I, V, VII, X, XII, VIII, and von Willebrand factor, increased plasminogen activator inhibitors 1 and 2, and decreased free protein S and activated protein C resistance); uterine compression of the inferior vena cava (IVC) and left iliac vein; progesterone-induced venous stasis; local trauma to pelvic veins during delivery; vascular endothelial injury and activation of the coagulation system during labour and delivery; and immobility or prolonged bed rest, especially after delivery; hence, the risk is 5 to 10-fold higher than non-pregnant women of comparable age [4,5,7,8]. The absolute risk of VTE is 0.1% antepartum and 0.05% postpartum [4], but the actual day-to-day risk is increased 15 to 35-fold postpartum, being greatest in the first 6 weeks but remains increased 2.2-fold in weeks 7–12 as compared with a similar duration one year later [4,5,7–9]. Furthermore, women with PA-VTE were younger and had less PE (19.7% versus 32.3%) and more left-sided DVT (73.9% versus 54.8%) compared with women who had non-PA-VTE [9]. Nevertheless, a Singaporean study on 89 VTE cases (with 18 cases of PE) reported only 29 (33%) cases occurring postpartum [10]. Antepartum VTE can represent recurrent VTE, found in 3.3% of the cases during early pregnancy before prophylaxis, or in 6.2% when not on prophylaxis, the risk being considerable with history of 2 or more previous VTE, hormone-related VTE, presence of antiphospholipid antibodies, and the need for long-term anticoagulation, whereas prophylactic or intermediate doses of low molecular weight heparin (LMWH) may not be sufficient in its prevention [5].

Risk factors for VTE in pregnant and postpartum women

There are pre-existing, new onset or transient, and obstetric risk factors. Although inherited thrombophilia can account for up to 50% of cases in pregnancy with reported odds ratio (OR) varying from 0.74 to 34.40 [4,5], the absolute rates remain small [7]. Non-inherited factors are more important individually, most common of which are hospitalization (10.4%), previous surgery (10.4%), and family history of VTE (9.3%) [9]. Risk factors have been classified into high, intermediate, and low-risk categories [11], with some being significant only in the postpartum period [12]. In the Danish nationwide cohort study on 1.3 million pregnancies, the independent effect of individual factors on the rate ratios (RR) of VTE varied in relationship to timing of the event and the presence of other factors [13]. Nevertheless, among cases of antenatal PE, only 70% had identifiable classical risk factors, and 4% ($n = 6$) had PE despite antenatal prophylaxis with LMWH but half of these 6 women received lower than the recommended doses, and 1.4% had recurrent PE in the same pregnancy [6]. Therefore, aside from the identification of risk factors, timely and adequate pharmacological prophylaxis is no less important.

An often-overlooked risk factor is race/ethnicity. Apart from Singapore [10], PA-VTE and associated mortality have been reported from Saudi Arabia where 60% of PA-VTE occurred postpartum with recurrence in 11% and mortality in 1.1% [14]; Rwanda, Africa, where the prevalence of proximal DVT in obstetric and gynaecological patients was 5.7% [15]; and Japan, where PA-PE increased 6.5-fold over a 10-year period, being 22-times greater in caesarean (CD) versus vaginal (VD) deliveries, resulting in 14.5% fatalities and mortality rate of 2.5/100,000 deliveries [16]. In addition, in Singapore, the prevalence was 1.81-fold higher in Malays compared with the Chinese [10]. Race/ethnicity can contribute to the risk of PA-VTE through pre-existing medical conditions like sickle cell anaemia, its inherent risk for VTE is increased further by factors such as splenectomy, central venous catheter insertion, low haemoglobin, and other biochemical abnormalities as described in the non-pregnant population [17]. Though data is lacking, such effects are likely to apply to PA-VTE too.

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The presentation of PE may not necessarily be preceded by DVT. In a study on 375 pregnancies with postpartum PE, 61.3% were diagnosed postpartum with no antenatal VTE, while only 2.7% were preceded by antenatal VTE, the rate of postpartum PE was 0.45/1000 deliveries, with 59.1% found in women readmitted to hospital [18]. In this study, PE accounted for 7 of the 40 maternal deaths in the study period (case fatality rate 2.2%) and ranked with amniotic fluid embolism as the leading causes of maternal death. The effect of the mode of delivery also varied with time, as the rate of PE following CD was higher than that following VD up to week 4, afterwards the rates for both approached background rates, while the transfusion of blood products increased the risk by 8.9-fold. Although the recurrence rate of previous VTE in pregnancy was 2.6%, the adjusted OR (aOR) was 4.31. In a French study on postpartum PE, the aOR declined progressively from 17.2 in weeks 1–2 to 1.9 in postpartum weeks 11–12, after which the increase was no longer significant [19]. Another study similarly found the aOR decreased from 12.1 in weeks 1–6 to 2.3 in weeks 7–12, and no longer significant from week 13 onwards [20]. These findings [4,5,7,8,18–20] indicated that the higher postpartum risk of VTE was compounded by mode of delivery and transfusion of blood products, and it declined with time until it was no longer significantly increased after 12 weeks.

In addition to medical risk factors, sociodemographic and anthropometric factors like advanced age, increasing parity, obesity, and smoking also increase the risk of PA-VTE. The reported risk factors [4–8,10,12,13,18,19,21–23] are shown in Table 1 with the RR, aOR, or absolute rate per 1000 cases where available.

Presentation and diagnosis of PE

The classical features of PE include shortness of breath (34.7%), tachycardia (30.4%), leg pain and/or swelling/weakness (9.6%), pelvic discomfort, and chest pain (13%) [4]. Shock, an uncommon presentation in the general population, defines a 3 to 7-fold increased mortality the majority of which were within 1 h of presentation [24]. Rapid integration of clinical findings and laboratory data, as well as a structured physiological approach to diagnosis and resuscitation, are necessary for optimal treatment in this “golden hour”, and echocardiography is important to differentiate shock states and reveal the characteristic features of PE [24]. Cardiac arrest can occur within 1–2 h after clinical presentation in two-thirds of fatal PE, and in these patients, transoesophageal echocardiography is helpful in diagnosis and indicates the need for thrombolysis in addition to cardiopulmonary resuscitation [24]. However, data on the prevalence and significance of shock in PA-PE are lacking. Clinical criteria such as the Wells and Geneva criteria based on non-pregnant individuals [25] are not widely adopted for risk categorization of pretest probability of PA-PE [4,26]. In one model, the most predictive risk factors included varicose veins, stillbirth, pre-eclampsia, postpartum infection, emergency CD, and medical comorbidities, but neither thrombophilia nor past VTE was assessed [4].

The best-studied blood test in PA-VTE is D-dimer assay, which has reported sensitivity of 73%–100% in retrospective studies in the general population, but its usefulness in pregnancy is limited due to the rising normal levels from <0.95 μg/mL in the first to <1.7 μg/mL in the third trimesters [4], thus leading to false-positive results, and although the negative predictive value remains accurate regardless of trimester, PA-PE has been documented despite normal D-dimer values [4,27]. Furthermore, D-dimer test may be positive in infection, trauma, and other inflammatory states [25], and it was non-validated in prospective diagnostic cohort studies in pregnancy [4]. Recently, it was reported that in post-CD women suspected of PE within 24 h postpartum, by raising the D-dimer recommended cut-off level of ≤500 ng/mL for VTE to 800 ng/mL, the number of patients excluded from suspected PE increased from 9.6% to 18.4% without additional false-negative results, thus reducing the number of unnecessary CT [28]. In a study using clinical signs of DVT, haemoptysis, and PE as the most likely diagnosis, together with D-dimer testing, CT pulmonary angiography (CTPA) was avoided in 65% and 32% during the first and third trimesters, respectively [29], suggesting D-dimer should be used in conjunction with clinical parameters. The utility of other biochemical tests like brain natriuretic peptide and troponin in risk stratification or diagnosis of PA-VTE remains to be established [4].

A diagnosis of DVT can be made by means of compression ultrasonography (CUS) with the accuracy of up to 98.7% [9]. In case of uncertainty, non-contrast MRI can be used to image pelvic and lower

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Table 1
Risk factors for venous thrombosis and pulmonary embolism in pregnancy.

Non-obstetric factors	VTE/PE		
Race/ethnicity – Malay versus Chinese	1.81 overall		
Blood group – non-O versus group O	3.19		
Previous VTE in pregnancy or on oral contraceptives*+	24.8		
Thrombophilia	Overall	Asymptomatic	Family study (/1000)
Protein S deficiency*+	7.0%	0.3%–6.0%	20, 0–6.6
Protein C deficiency*+	0.5%	0.4%–6.0%	20, 0–1.7
Antithrombin deficiency*+	0.6%	0.4%	20, 3.0–14.3
Factor V Leiden mutation (homozygous)*+	1.0%	3.4%–14%	70, 14.0
Factor V Leiden mutation (heterozygous) *+	3.0%	0.8–40%	15, 3.1
Prothrombin mutation G20210A (homozygous)*+	1.0%	26/1000	70
Prothrombin mutation G20210A (heterozygous)*+	8.0%	6/1000 -17%	15, 2.6
Antiphospholipid syndrome*+	–	–	–
	Antepartum risk	Postpartum risk	
Medical comorbidities			
Diabetes	3.08§	2.0§	
Inflammatory bowel disease	3.46§	4.56§	
Cardiac disease	–	6.58, 7.1§	
Systemic lupus erythematosus	–	8.83, 8.7§	
Hypertension	–	1.8§	
Sickle cell disease+	–	6.7§	
Age ≥35 years, 35–44 y	1.42§	1.51§	
≥40 years	–	1.67§	
Smoker, Smoking 10–30/d, 5–9/d	5.44, 2.1§	1.31, 3.4/2.0§	
Acute respiratory infection	–	1.65§	
Varicose veins	2.69§	3.83§	
Pregnancy related			
Assisted reproduction technology (first trimester PE)	4.6§	1.8§	
Previous births ≥3	2.84§	2.07, 1.49§	
Parity >1	4.03§	1.5§	
Hyperemesis hospitalization (vs no hospitalization)	2.5§	1.9, 2.5§	
BMI 25.0–29.9, 30–34.9, ≥35 (versus normal)+	1.4, ns, ns§	1.7, 2.1, 3.5§	
BMI <25 kg/m^2, >25 kg/m^2, >30 kg/m^2	1.8 (≥25)§	3.75 (≥30)§	
Obesity	2.51, 2.65 (≥30)§	2.4, 1.8, 5.3§	
	–	1.7§	
Weight gain >21 kg (versus 7–21 kg)	–	1.6§	
Multiple pregnancy (versus singletons)	2.8, 2.6§	4.2§	
Infection (antibiotic treatment versus no treatment)	1.8§	1.3§	
Infection (discharge diagnosis versus no infection)	4.3§	2.4, 20.2/6.2(VD/CD)§	
Infection postpartum (antibiotic treatment versus no)	–	1.4§	
Infection postpartum (discharge diagnosis versus no)	–	5.0§	
Urinary tract infection	1.88§	–	
Infection and other factors	–	2.7§	
Bleeding, plus other factors	–	2.1, 3.4§	
Anaemia	–	2.6§	
Threatened preterm labour, plus other factors	–	3.4§	
Preterm delivery (<37 weeks)	–	2.18, 2.69, 5.06§	
Hospitalization (1–2, 3–7, 8–14, >14 d versus no)	10.3, 12.2, 4.0, 3.3§	1.5, 1.4, 4.2, 5.9§	
Hospitalization with pre-eclampsia, plus other factors	–	5.0, 6.4§	
Pre-eclampsia	–	5.8 (with FGR), 3.1§	
Pregnancy hypertension	–	2.06§	
Hospitalization with foetal growth restriction/death	–	5.6 (plus other)§	
Foetal growth restriction	–	3.8§	
Stillbirth	–	6.24, 5.97§	
Antepartum haemorrhage	2.3§	–	
Caesarean delivery (CD) - (inclusive)+	–	1.99, 3.58§	
CD without labour (versus vaginal delivery)+	–	2.1, 3.11§	
Emergency/intrapartum CD (versus VD)+	–	3.0, 3.70§	
Obstetric haemorrhage	–	2.89§	
Major postpartum haemorrhage (versus no bleeding)	–	1.4§	
PPH (≥1000 mL)	–	12.0/4.1§ (surgery/no)	

(*continued on next page*)

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Table 1 (*continued*)

Non-obstetric factors	VTE/PE	
Transfusion – packed cells/whole blood	–	3.93, 7.6§
Transfusion – other blood products	–	8.24§
Immobility^{+} (strict bedrest ≥1 week) - BMI ≥25 kg/m^2	62.3§	40.1§
Immobility^{+} (strict bedrest ≥1 week) - BMI <25 kg/m^2	7.7§	10.8§

Note: Result expressed as risk ratio/adjusted odds ratio §, or absolute rate/1000, or % as indicated.
BMI = body mass index, CD = caesarean delivery, VD = vaginal delivery, PPH = postpartum haemorrhage, FGR = foetal growth restriction.
Data compiled from the following references [4-8,10,12,13,18,21-23]
Thromboprophylaxis indicated - * antepartum, $^{+}$ postpartum.

extremity veins [7]. However, if there is suspicion of PE already, it may be faster to proceed directly to examine the pulmonary vasculature (see later).

Echocardiography, both transthoracic and transoesophageal [9], may be helpful in initial assessment, especially in a patient with shock [24]. In non-pregnant patients, echocardiography can document features of right ventricular dysfunction and failure, and right heart emboli-in-transit in up to 17% of acute PE, including the long, thin, extremely mobile thrombi characteristically found in the right atrium (type A) which originate in the peripheral deep venous system and comprise the high-risk group of severe PE of which one-third were fatal within 24 h, the high mortality (≥50%) being associated with medical management as compared to the 15% mortality with surgical management; and the smaller, round, or oval-shaped type B thrombi which arise in the right ventricle and associated with good prognosis. Where there is available expertise, echocardiography can be considered in severe PE.

Chest X-ray (CXR) is the first radiological study in most cases, as it is easily accessible and can rule out unsuspected lung lesions and diseases, providing a clue to the likelihood, but not to confirm the diagnosis, of PE.

Confirmation of PE depends mostly on CTPA and lung scintigraphy (ventilation-perfusion or V/Q scan) [7]. For the former the median negative predictive value was 100%, sensitivity was 83%, and the frequency of inconclusive results was 5.9%; whereas for the latter, the respective values were 100%, 100%, and 4.0%, on a median prevalence of PE of 3.3% [30]. The advantages of CTPA include high sensitivity and specificity, short acquisition time and ease of access and interpretation, capacity to definitely depict clot and provide an alternative diagnosis, but the disadvantages include an increased non-diagnostic rate due to physiological changes in pregnancy, high maternal breast radiation dose (can be reduced by shielding), inherent false-positive and false-negative rates, especially in low and high-risk patients, and the risk associated with iodinated contrast material [27]. The advantages of V/Q scan include radionuclide being safe in pregnancy, low maternal breast radiation, low non-diagnostic rate in pregnant patients, and a diagnostic rate of 97% in those with normal CXR and no history of asthma or chronic lung disease, the radiation dose can be reduced by 50% in the perfusion component as well as eliminating the ventilation scan if the perfusion scan is normal, and it can be used in patients with contrast material allergy or impaired renal function, but the disadvantages include the inability to provide alternative diagnosis in the absence of PE, long acquisition time, and 3–25% non-diagnostic rate [27]. Overall, the nondiagnostic study was slightly more common with CTPA (17.0% versus 13.2%) and more likely in the presence of a normal CXR (aOR 5.4) compared with the V/Q scan [31].

Imaging studies should be combined with blood tests to enhance diagnosis. The pregnancy-adapted YEARS diagnostic algorithm has been proposed for suspected PA-PE, which can avoid CTPA in 39% of patients [2,26]. In terms of imaging studies, the positive likelihood ratios for a diagnostic test were 18.3 for high probability V/Q scan, 24.1 for spiral CT, and 16.2 for CUS [32]. In patients with a moderate or high pretest probability, these findings were associated with >85% post-test probability of PE. The negative likelihood ratios were 0.05 for normal or near-normal lung scan, 0.04 for negative spiral CT along with negative CUS, and 0.08 for D-dimer concentration of <500 μg/L, yielding a post-test probability of PE below 5% in patients with a low or moderate pretest probability [32]. In a multicentre multinational prospective diagnostic management outcome study on the diagnosis of PA-PE, using pretest clinical probability assessment, high-sensitive D-dimer testing, bilateral lower limb CUS, and CTPA, PE was diagnosed in 7.1% among 391 women, and the rate of symptomatic VTE events

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was 0% among untreated women after the exclusion of PE on the basis of negative results, but PE could be ruled out without CTPA in only 16% of pregnant women on this basis [33].

The following management approach as recommended [34] by the American Thoracic Society and the Society of Thoracic Radiology and endorsed by the American College of Obstetricians & Gynecologists is simple and straightforward.

(1) Not to use D-dimer to exclude PE in women with suspected PE;
(2) Perform bilateral lower extremities CUS in suspected PE with signs/symptoms of DVT, start anticoagulation treatment if CUS is positive, and arrange further testing if CUS is negative;
(3) In suspected PE without signs and symptoms of DVT, study the pulmonary vasculature rather than performing CUS of the lower extremities;
(4) In suspected PE, perform CXR as the first radiation-associated procedure;
(5) If the CXR is normal, perform lung V/Q scan as the next imaging test;
(6) If the V/Q scan is nondiagnostic and a decision is made to further investigate, perform CTPA rather than digital subtraction angiography;
(7) If there is suspicion of PE and the CXR is abnormal, perform CTPA as the next test.

Treatment and prevention

Women with suspected PA-VTE should be admitted for assessment, monitoring, and initiation of treatment.

If shock is present, intubation and fluid resuscitation should be undertaken judiciously. Intubation may cause cardiac decompensation, volume expansion with crystalloid solution to treat hypotension can also precipitate further deterioration, and norepinephrine is the preferred vasopressor for severe shock, whereas dobutamine should only be considered in case of moderate hypotension with appropriate monitoring [24]. Unloading the right ventricle with pulmonary vasodilator (inhaled prostacyclin and nitric oxide) may be a useful adjunct to thrombolysis in patients with right ventricular failure and contraindications to thrombolysis or awaiting embolectomy [24].

The primary treatment is anticoagulation with LMWH which has greater reliability and fewer adverse effects, including heparin-induced thrombocytopenia, osteoporosis, and bleeding, than unfractionated heparin (UFH), both of which do not cross the placenta [2,5,7,8]. The dosing is titrated to achieve anti-factor Xa levels at 4 h post-dose of between 0.6 and 1.0 U/mL, and 1.0–2.0 U/mL, for twice-daily and once-daily regimens, respectively [5]. The alternative is weight-adjusted LMWH dosing with subcutaneous enoxaparin at 1 mg/kg twice daily or 1.5 mg/kg once daily, or dalteparin at 100 U/kg twice daily or 200 U/kg once daily [5,8]. In renal dysfunction with creatinine clearance of <30 mL/min, UFH is preferred [5], usually with an initial bolus of 5000 U intravenously followed by 10,000 U or more subcutaneously every 12 h to maintain the aPTT at 1.5–2.5 times control measured at 6 h after injection, or a mid-dosing interval target of 0.3–0.7 U/mL in the *anti*-Xa assay [5]. A decrease in dosing intensity later in therapy to 75% of a full treatment dose may be considered if there is anticoagulant-related bleeding or heparin-induced osteoporosis [8].

In the management of labour and delivery, neuraxial anaesthesia should be avoided if labour commences when therapeutic dose anticoagulation is given, but it can be administered 12 h and 24 h after the last prophylactic and therapeutic dose, respectively, of LMWH, whereas intravenous UFH should be stopped 6 h, or a minimal interval of 12 h if UFH is given at 7500 or 10,000 U twice a day, before labour induction [5,8]. A normal aPTT is necessary before neuraxial anaesthesia. Postpartum resumption of prophylactic or therapeutic dose of LMWH should be delayed for at least 12 h and 24 h, respectively, after the neuraxial block or at least 4 h after removal of the epidural catheter [5,8].

Postpartum continuation of anticoagulant therapy is important, and LMWH can be reinitiated 6 and 12 h after VD and CD, respectively, in the absence of persistent bleeding for at least 6 weeks postpartum, and a total treatment duration of 3 months [1,2,5,23]. Both LMWH and UFH are safe for breastfeeding [5,7,8].

Patients with massive PE are high-risk as they are haemodynamically unstable or severely hypoxaemia, requiring aggressive reperfusion therapies and mechanical or systemic thrombolysis [3,4]. Thrombolytic therapy may be lifesaving as maternal mortality was as high as 55% [7], and usually does

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not increase maternal or foetal complications in the absence of contraindications [4]. Although in case series maternal mortality was 8% [4], survival rate could be as high as 94%, despite the risk of major bleeding in 17.5% and 58.3% during pregnancy and in the puerperium, respectively, with 12.0% foetal death [5]. Systemic thrombolysis with recombinant tissue plasminogen activator (tPA) such as alteplase 100 mg over 2 h, or streptokinase or urokinase, produces good results [3,4]. This can be given intravenously or directly into the pulmonary arteries via a catheter, leading to fragmentation of the clot, relieving the obstructive shock, and alleviating the haemodynamic instability [3]. Owing to the risk of major and intracranial bleeding, routine thrombolysis should be avoided for intermediate or low-risk PE [3]. The major risk is maternal bleeding in 8% of patients [4], and placental but mostly intrapartum bleeding is the main problem and all major postpartum bleeding occurred with thrombolysis used within 72 h of delivery, while the risk of foetal and neonatal death was 18.5% [3]. Catheter-based thrombolytic administration may have lower complication risk as lower dosages are used, but data in pregnancy are lacking [4]. Surgical embolectomy, performed with cardiopulmonary bypass by removing proximal pulmonary clots through incisions of the two main pulmonary arteries, is least commonly used and is restricted to salvage situations [3]. Maternal survival was reported to be 84%–86.1%, and major bleeding and foetal death were both 20% [3,5]. In one series of 8 cases, there were no maternal deaths, but there were 3 foetal deaths (37.5%) and 4 preterm births (50.0%) [4]. Owing to the concern with major postpartum bleeding and about half of severe PE occurred within 24 h of delivery, surgical or catheter embolectomy are potentially life-saving alternatives postpartum [5].

Vitamin K antagonists (VKA) such as warfarin should be avoided during pregnancy due to its multiple adverse foetal and teratogenic effects (3.7%–6.4%), and it should be replaced by LMWH if pregnancy is planned or as soon as it is diagnosed [4,5,7,8]. It is not contraindicated in breastfeeding and can be considered for prophylaxis or as the continuation of treatment after delivery, commencing VKA at least one day after restarting of LMWH to avoid double anticoagulation immediately after delivery, and discontinuing LMWH when the international normalized ratio is > 2.0 [2]. Direct oral anticoagulants should be avoided as its safety in both pregnant and postpartum breastfeeding women is not established [2].

In haemodynamically unstable PE patients, extracorporeal membrane oxygenation (ECMO) is an alternative to thrombolysis in restoring haemodynamic stability [4], but it is not a reperfusion therapy per se [3]. Using a modified cardiopulmonary bypass circuit, ECMO oxygenates and decarboxylates venous blood through a semi-permeable membrane and returns the blood to either the venous circulation (veno-venous or VV-ECMO for respiratory function) or the arterial circulation (veno-arterial or VA-ECMO, for respiratory and cardiac functions) [3]. In high-risk PE, VA-ECMO is used. In pregnant women, ECMO is mostly used to treat refractory hypoxaemia in acute respiratory distress syndrome with a veno-venous circuit [3], with PE accounting for only 5% of the obstetric cases requiring ECMO. Considering all indications of VA-ECMO, 30-day maternal survival was 72.4%, bleeding occurred in 12–16% with the majority receiving therapeutic anticoagulation, and >70% women with VV and VA-ECMO had a live birth during or after ECMO [3]. In general, ECMO is useful in refractory cardiac arrest, as a bridge to reperfusion therapy, or where reperfusion therapies are contraindicated or unavailable, in association with heparin [3].

A temporary retrievable IVC filter may be indicated in acute PA-DVT where there is absolute contraindication for anticoagulation, and in patients with extensive iliofemoral venous thrombosis within 2–4 weeks prior to expected delivery [4,5,8]. The filter is placed suprarenally to avoid compression by the gravid uterus and the 10% risk of filter migration, fracture, and wall penetration, as well as protecting against embolization of an ovarian vein thrombosis [3,4]. Other indications are iliac vein DVT or recurrent VTE (within 2 weeks) prior to planned delivery [8]. The complication and failure-to-retrieve rates were 8.87% and 11.25%, respectively, and complications include thrombosis of the filter (2.3% versus 0.9%) and perforation of the IVC (7.0% versus 4.4%), while failure to retrieve the filter was 26% versus 11%, compared with the general population, but the rate of PE was 0% so that this is an acceptable option, and it should be removed as soon as clinically feasible afterwards [5]. Although a review on 124 pregnancies showed no fatal PE and no recorded foetal morbidity or mortality in patients treated with IVC filters, there were concerns with complicated retrieval of the filter during pregnancy [4].

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General supportive treatment, including prevention of dehydration especially postpartum, early and continued ambulation especially after CD, and prophylaxis with pneumatic compression devices or graded compression stockings [4] applied from the time of admission or bedrest until the woman is ambulant, are useful measures. Attention should also be paid to maternal psychological well-being due to the risk of postpartum depression.

Prophylaxis is essential for most at-risk women. Pre-pregnancy counselling allows risk assessment, and the regimen can be individualized. The preferred agent is LMWH which is associated with live-births in 94.7%, VTE or arterial thrombosis in 0.86%, and significant bleeding in only 1.98% [5]. Patients with history of oestrogen-related or unprovoked VTE not on chronic treatment should receive antepartum and postpartum thromboprophylaxis with either low-dose prophylactic- or intermediate-dose LMWH, whereas patients with history of provoked VTE should receive postpartum thromboprophylaxis. The low-dose regimen is dalteparin is 5000 U once daily or enoxaparin 40 mg once daily. Intermediate dose regimen is dalteparin 5000 U twice daily or 10,000 U once daily, or enoxaparin 40 mg twice daily or 8 low-dose 0 mg once daily [8]. The dose is adjusted to maintain a peak *anti*-Xa level of 0.2–0.6 units/ml [8]. Prophylactic LMWH is withheld 24 h prior to delivery or neuraxial anaesthesia. However, VTE can develop, despite LMWH prophylaxis in 4.3% [5], and the risk of PPH was 30% versus 18% in those who did not receive LMWH, although the risk of severe PPH after VD was similar at 5.6% versus 5.0%, respectively, while the PPH risk after CD was 12% versus 4% in non-users [5]. Compared with planned induction of labour, women with spontaneous labour who delivered within 24 h after the last dose of LMWH had 1.9-fold increased risk of PPH, thus planned induction of labour is preferrable [5]. For patients allergic to heparin, fondaparinux may be used [4]. As an alternative for postpartum thromboprophylaxis, a VKA such as warfarin can be considered with adequate bridging until the international normalization ratio is in the therapeutic range, and the postpartum bleeding risk has subsided, such as 5 days after delivery [5].

Scoring systems have been designed to guide thromboprophylaxis in high-risk pregnant populations. In one study, a score of 0.5–3.0 is assigned to individual risk factors which are mostly related to past or family history of VTE and inheritable factors, and medical thromboprophylaxis is recommended from a score of $\geq$1.0 [35]. Another study utilizing similar parameters plus several additional demographic factors to construct a risk score for women who had CD found that the risk score model proved effective in avoiding pharmacological prophylaxis in 46.5%, although one of these women developed a DVT (0.2% of total but 0.9% of the low-risk group without prophylaxis) [36]. As most of the risk factors related to the pregnancy, incidental and obstetric complications, as well as conditions related to delivery, are not included in these models, such scoring systems may have limited application in the majority of pregnant women without relevant family or past history. Furthermore, the predictive value of the score can be negated by new complications and events around delivery, so that its usefulness may be limited in practice.

Post-pulmonary embolization syndrome

Long-term suboptimal cardiac function, or impaired pulmonary artery flow dynamics or pulmonary gas exchange at rest or during exercise, together with persistent dyspnoea, exercise limitation, and impaired functional status or quality of life (QOL) without an alternative explanation, which persist for 3 months or more after effective anticoagulation, have been found in up to 50% of patients [26,37,38]. This post-PE syndrome may be due to chronic thromboembolic pulmonary hypertension (CTEPH) which is the most severe form affecting 3% of PE survivors after 6-months treatment, its risk factors include diagnostic delay, high thrombus load, recurrent symptomatic PE, pulmonary hypertension or RV dysfunction at baseline, and failure to achieve thrombus resolution, and the diagnosis is based on planar V/Q scan demonstrating raised mean pulmonary artery pressure with thrombotic pulmonary vascular obstruction [26,37,38]. Bilateral pulmonary endarterectomy is curative but lifelong anticoagulation may be required due to recurrent PE risk [26]. Another cause is chronic thromboembolic disease (CTED), an intermediate phenotype with symptoms which correlated with the 6-min walk test, but exercise limitation was not correlated with baseline residual pulmonary obstruction, pulmonary function testing, or echocardiographic results [26,39]. Predictors identified included age, BMI, and smoking history, and the underlying cause of CTED may be general

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deconditioning [26,39]. A third category is dyspnoea with functional limitations without identifiable pulmonary vascular disease (post-PE-related dyspnoea) [37,38]. The exercise limitation, dyspnoea, and impaired QOL could be found one year later in non-obstetric patients [39], and for a median follow-up interval of 3.6 years in another study even though no single independent determinants of dyspnoea were found [40]. Although there is no literature on post-PE syndrome following PA-PE, the considerable risk of post-thrombotic syndrome after DVT in pregnancy and the puerperium with reduced QOL and higher mortality during the first year compared with the general population [41] suggests a similar risk for post-PE syndrome after delivery, and further studies on this issue are warranted.

Lastly, women with PA-VTE still had significantly increased event rates in all-cause mortality (3.86), recurrent VTE (5.19), major bleeding (2.65), and any bleeding (13.85), whereas there was reduced myocardial infarction (0.09) and stroke (0.18), up to 12 months later [9]. As well, the risk of postpartum depression can conceivably be aggravated by the additional stress of recovering from PE, need for continued anticoagulant treatment, other adverse events [9], and post-PE syndrome, on top on the stress of motherhood. These areas should be addressed in future studies.

Conclusion

Though relatively uncommon, PA-PE is still more frequent than PE in non-pregnant women of comparable age and remains a leading cause of maternal mortality in developed countries. As an initially low-risk woman could undergo risk escalation during pregnancy and after delivery, vigilance, prompt diagnosis, and appropriate treatment are vital in improving maternal and perinatal outcome. Uncertainties and questions still exist in many areas. Further studies are warranted to clarify these issues, especially in the presence of an increasing trend in recent years.

Summary

PE is a serious complication in pregnancy and a leading cause of maternal mortality. Pregnancy-related physiological changes, complications, delivery mode, and management, including blood transfusion, all serve to predispose women toward PE, on top of any risks from hereditary and acquired thrombophilias, medical comorbidities, and sociodemographic and anthropometric factors. Continued vigilance is necessary to identify the women with increased or increasing risk, arrange timely and reliable diagnostic imaging studies, and commence appropriate and effective treatment promptly upon diagnosis. In addition to the standard anticoagulation therapy, additional and alternative therapies which include thrombolysis, embolectomy, and even ECMO, may be necessary and lifesaving. In women at risk of venous thrombosis and PE, such as those with past history or family history, or history of thrombophilia, or following certain pregnancy complications and/or interventions, prophylactic anticoagulation is indicated starting from the antenatal period or after delivery and continued for at least 6 weeks postpartum. Other safe general and supportive measures are useful even after discharge from hospital. Breastfeeding is safe in women on the standard anticoagulant therapies. Although the literature on postpartum mood changes and post-PE syndrome is wanting, these problems are likely to be at least as frequent as in the non-pregnant populations, and these women should be followed up for early detection, possible treatment, and counselling on the risk of future pregnancy and contraception.

Conflict of interest

The author has no conflict of interest to declare.

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Practice points

- For diagnosis, a ventilation-perfusion scan can be performed first due to its safety, low non-diagnostic rate, reduction of radiation dose is possible, and the ventilation scan can be omitted if the perfusion scan is already diagnostic.
- CT pulmonary angiography is faster to produce a result, has a better capacity to definte clots, as well as the ability to provide an alternative diagnosis in case it was not pulmonary embolism, but the downside is a higher non-diagnostic rate in pregnancy.
- Low molecular weight heparin is the preferred anticoagulant for both treatment and prophylaxis, and its dose is best titrated on the basis of the post-dose anti-factor Xa level.
- In severe pulmonary embolism and shock, systemic or catheter-based thrombolysis with recombinant tissue plasminogen activator, streptokinase, or urokinase may be lifesaving.
- Patients with completed anticoagulant therapy should still be followed up for at least one year for the diagnosis and mitigation/treatment of sequelae which include post-pulmonary embolization syndrome, increased adverse health events, and depression.

Research agenda

- The design of a pregnancy-specific risk-prediction score based on the evolution of incidental and pregnancy complications and mode of delivery on top of sociodemographic and anthropometric factors for the early detection and treatment of venous thromboembolism.
- The epidemiology of post-pulmonary embolization syndrome and its underlying pathophysiology in women who have been treated for pregnancy-associated pulmonary embolism.
- Whether a diagnosis of and treatment for pregnancy-associated pulmonary embolism would increase the risk of postnatal depression or impact on maternal bonding with and care of the offspring.

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